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An Expedient New Synthesis of Substituted Carbazoles via α-Oxoketene Acetals through Heteroaromatic Annelation Methodology

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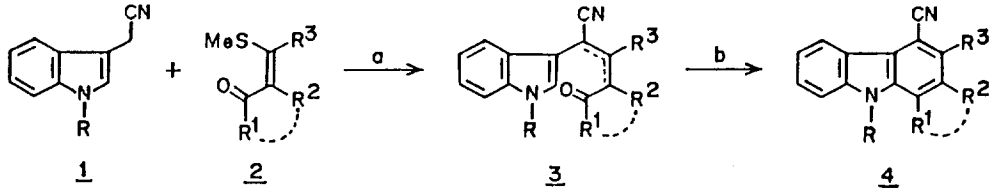
Abstract: A new general method for substituted carbazoles **4a-x** has been developed involving base induced conjugate addition-elimination sequence of indole-3-acetonitriles **1** to various α-oxoketene S,S-,O,S- and N,S-acetals **2a-x** followed by cyclization of the intermediates **3** with *p*-toluenesulfonic acid in refluxing benzene. © 1997 Published by Elsevier Science Ltd.

Development of efficient methods for the synthesis of carbazole and its derivatives is of current interest since increasing number of carbazole alkaloids of natural origin have displayed varied biological activities.[1] Many synthetic methods for this group of compounds have been developed starting from 1,2,3,4-tetrahydrocarbazoles, biphenyls, diphenylamines and 2-(*o*-aminoaryl)cyclohexadiene iron tricarbonyls.[1d,2] Recently a number of approaches involving [*b*]-annelation of indoles have been developed.[1e,1f,3] Many of these methods suffer due to overall poor yields and harsh reaction conditions. Besides, the structural features of many naturally occuring cabazoles isolated recently display characteristic C-ring substituent distribution making these methods inadequate to achieve the synthesis with less number of steps with improved yields.

In continuation of our studies on aromatic and heteroaromatic annelation,[4] we became interested in drawing a general synthetic strategy for carbazoles as formulated in scheme-1. We have choosen indole-3-acetonitriles **1** as strategic allyl anion components and α-oxoketene S,S-,O,S- and S,N-acetals **2**[5] as 1,3-dielectrophilic 3-carbon fragments. The choice of substituents on **2a-x** thus will control C-ring regiochemistry of the product carbazoles. We have successfully extended our heteroaromatic annelation protocol for the synthesis of a large number of these carbazoles in very high yields just within two steps. We report our preliminary results in this communication.

In a typical experiment, **1a** (10 mmol) was added to a suspension of NaH (20 mmol) in dry DMF at 0°C with stirring for 1hr, followed by dropwise addition of **2a** (10 mmol) in dry DMF (10 min). The reaction mixture was continued stirring at rt (10 hr) followed by work up to yield **3a** in 96% yield following exclusively 1,4-addition-elimination sequence. The intermediate **3a** was then cyclized in the presence of TsOH in refluxing benzene to yield after work up the corresponding carbazole **4a** in 96% yield.[6] Similarly the oxoketene dithioacetals **2b-i** were reacted with **1a** & **b** to yield the corresponding

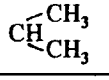
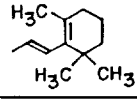
carbazoles **4b-l** in 69-92% overall yields.[6] Interestingly **2p** reacted with **1a** under similar reaction conditions to yield directly the corresponding carbazole-1-aldehyde **4p** in 69% yield involving *insitu* hydrolysis of the acetal group.



a: NaH, DMF, 0°C - RT; b: TsOH, C_6H_6,Δ

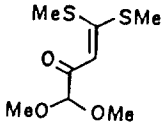
Scheme 1

Table

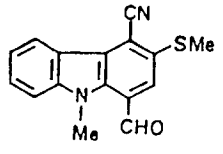
4	R	R^1	R^2	R^3	m.p. °C	Yield %
a	CH_3	CH_3	H	SCH_3	146-147	96
b	$CH_2C_6H_5$	CH_3	H	SCH_3	146-147	82
c	CH_3	CH_3	CH_3	SCH_3	177-178	92
d	$CH_2C_6H_5$	CH_3	CH_3	SCH_3	129-130	81
e	CH_3	C_6H_5	CH_3	SCH_3	176-177	72
f	$CH_2C_6H_5$	C_6H_5	CH_3	SCH_3	176-177	82
g	CH_3	C_6H_5	H	SCH_3	138-139	69
h	CH_3		H	SCH_3	134-135	85
i	CH_3		H	SCH_3	132-133	82
j	CH_3	CH_3	CH_3	OCH_3	138-139	92
k	$CH_2C_6H_5$	CH_3	CH_3	OCH_3	154-155	85
l	CH_3	C_6H_5	H	OCH_3	164-165	72
m	CH_3	C_6H_5	H		120-121	71
n	CH_3	C_6H_5	H		189-190	79
o	CH_3	*p*-$OCH_3C_6H_4$	H		158-159	62

Many natural carbazoles carry methoxy group at 3-position as substituent and thus we considered of interest to react the α-oxoketene O,S-acetals **2j-l** with **1** to yield the corresponding 3-methoxy carbazoles. The O,S-acetals **2j-l** were reacted with **1** under similar reaction conditions to yield the corresponding 3-methoxy carbazoles **4j-l** in 72-92% overall yields.[6] The carbazoles **4j & k** are direct derivatives of carbazomycin-B and the conversion of **4k** to carbazomycin-B is in progress. As a further strategy to utilize the method for the synthesis of 3-aminocarbazoles, the α-oxoketene S,N-acetals **2m-o** were reacted with **1a** under similar reaction conditions to yield the corresponding 3-aminocarbazoles **4m-o** in 62-79% overall yields.[6]

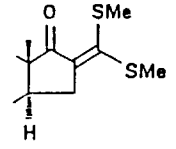
When the cyclic oxoketene dithioacetals **2q-s,t-w** were reacted with **1a** in similar manner, the corresponding [*a*]-annelated carbazoles **4q-s,t-w** were obtained in 78-92% overall yields respectively.[6] Interestingly, the oxoketene dithioacetal **2x** derived from estrone-3-methylether as reported earlier,[7] reacted with **1a** under similar reaction conditions to yield the corresponding carbazole **4x** in 78% yield as a pure enantiomer with a rotation $[\alpha]^{13}_{D}$ +49° (c=1, dioxane). Thus the method is of considerable synthetic interest to prepare various enantiomerically pure carbazoles starting from appropriate optically active α-oxoketene dithioacetals.



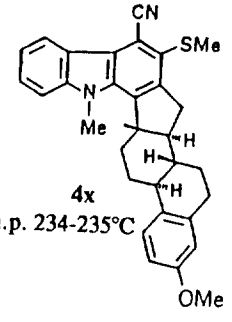
2p



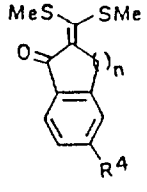
4p
m.p. 187-188°C



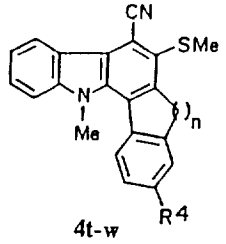
2x



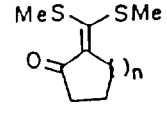
4x
m.p. 234-235°C



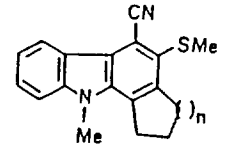
2t-w



4t-w



2q-s



4q-s

4	t	u	v	w
n	1	2	2	3
R^4	H	H	OMe	H
m.p.°C	185-186	203-204	149-150	142-143

4	q	r	s
n	1	2	3
m.p.°C	179-180	158-159	173-174

From these studies it may be concluded that the extension of our heteroaromatic annelation methdology provides most efficient and expedient synthetic route for making carbazoles with greater control on regiochemistry of C-ring substituents. Further work on these studies is in progress.

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6. Structure of all compounds prepared were confirmed with the help of spectral and analytical data. Representative spectral and analytical data for compounds **3a**, **4a**, **4m** and **4k** are given below.

3a: Colourless crystals (chloroform-ether); mp. 112-113°C; IR (KBr): 2201, 1712; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.27 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 3.79 (s, 3H, NCH_3), 4.00 (s, 2H, CH_2), 7.18-7.32(m, 3H, ArH), 7.34 (s, 1H, ArH), 7.83 (d, 1H, J=8 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.13,29.28,33.11,49.15,103.34,106.76,109.62, 118.36,120.14,120.30,122.55,125.74,130.25,136.38,149.58,202.72;MS (m/z): 284 (M^+, 38.5%), 194 (100%). Anal. Calcd. for $C_{16}H_{16}N_2OS$ (284.22): C, 67.56;H, 5.67;N, 9.86.Found: C, 66.72;H, 5.63;N, 9.82.

4a: Colourless crystals (chloroform-hexane); IR (KBr): 2206; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.53(s, 3H, SCH_3), 2.74 (s, 3H, CH_3), 3.87 (s, 3H, NCH_3), 6.99 (s, 1H, ArH-H_2), 7.18-7.26(m, 2H, ArH), 7.43-7.49(m, 1H, ArH), 8.49 (d, 1H, J=8 Hz, ArH-H_5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.45,20.70,32.09,102.98,108.76,117.47,119.79,121.39, 124.09, 126.09, 127.36, 129.56, 132.18, 137.67, 141.93; MS (m/z): 266 (M^+, 100%). Anal. Calcd. for $C_{16}H_{14}N_2S$ (266.21): C, 72.13;H, 5.30;N, 10.52.Found : C, 72.02;H, 5.27;N, 10.46.

4m: Brown crystals (hexane); IR (KBr): 2208; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.22 (t, 4H, J=4.5 Hz, NCH_2), 3.31 (s, 3H, NCH_3), 3.95(t, 4H, J=4.5Hz, OCH_2), 7.00(s, 1H, ArH-H_2), 7.24-7.33(m, 2H, ArH), 7.45-7.54(m, 6H, ArH), 8.70(d, 1H, J=8 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.82,53.17,67.26,97.53,109.13,117.97,119.30,119.83, 120.60,121.88,125.23,127.64,128.24,128.30,129.49,131.04,134.53,138.96,143.20,149.29;MS (m/z): 367 (M^+, 100%). Anal. Calcd. for $C_{24}H_{21}N_3O$ (367.45): C, 78.45,H, 5.76,N 11.44.Found: C, 78.58;H, 5.72;N, 11.38.

4k: Colourless crystals (ether); IR (KBr): 2217; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.21(s, 3H, CH_3), 2.37(s, 3H, CH_3), 3.91(s, 3H, OCH_3), 5.44(s, 2H, NCH_2), 6.90-6.93(m, 2H, ArH), 7.10-7.36(m, 6H, ArH), 8.55(d, 1H, J=8 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): w 12.86,15.58,48.53,62.26,94.68,109.20,116.98,119.90,120.65,121.00,121.44,125.28, 126.61,127.12,127.30,127.54,128.87,135.96,137.99,142.52,155.39;MS (m/z): 340 (M^+, 56.3%); 91 (100%). Anal. Calc. for $C_{23}H_{20}N_2O$ (340.42): C, 81.15;H, 5.92;N, 8.23.Found: C, 79.98;H, 5.86;N, 8.16.

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